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EXAMINER
ALLEN, M

ART UNIT	PAPER NUMBER
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DATE MAILED: 06/07/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474..
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 21-23, 25-27, 29-30 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 21-23, 25-27, 29-30 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

Claims 16-20, 24, and 28 have been canceled. Claims 21-23, 25-27, and 29-30 are under consideration by the Examiner.

Applicant's arguments filed 13 January 1995 in the amendment after final rejection (now entered) have been fully considered but they are not deemed to be persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as the specification, as originally filed, does not provide support for the invention as is now claimed.

The claims have been amended to recite "in a native conformation" and "under conditions where no crystals are formed."

Applicant has pointed to basis for the crystallization limitation in example 4 at pages 15-16. This example teaches conditions where crystals are formed. Applicant has extrapolated from this example to claim a method lacking the final crystallization step; however, the specification clearly contemplates crystallizing the protein as in Example 4. A method without crystallization is not contemplated. The specification does not tell how to use the uncrystallized form to produce insulin. All of the examples use the crystallized mono-Arg insulin for the production of insulin.

Furthermore, the specification exemplifies how to crystallize the protein and applicant implies in the arguments that omission of phenol, citric acid and/or zinc chloride from the final incubation buffer will result in no crystals being formed. However, this is not an adequate description of other conditions embraced by the claims where crystals will not be formed.

No basis has been pointed to for the limitation "in a native conformation." It is not known from the specification what this limitation means. It is not clear that a miniproinsulin has a "native conformation" as it is an insulin precursor form not found in nature. Furthermore, the steps of the examples appear to refold the protein following cyanogen bromide cleavage which liberates the miniproinsulin from its fusion partner thus indicating that it is not in a "native conformation" following liberation. Clarification is requested.

Claims 21-23, 25-27, and 29-30 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 29 and 30 are rejected under 35 U.S.C. § 102(e) as being anticipated by Grau (U.S. Patent No. 4,639,332).

Claims 29 and 30 are directed to mono-Arg insulin compounds produced by a recited process.

Grau teaches methods of preparing the claimed mono-Arg insulin

using methods that differ from those recited. However, the products would appear to be the same. The mono-Arg insulin of formula II is the embodiment of Grau where Y is Phe, X_n is Arg, and R^{30} is Ala otherwise identified as the preferred embodiment human insulin-ArgB31. (See abstract, column 2, Example 2, and claims.)

With regard to the above rejection, the Patent and Trademark Office does not have facilities for examining and comparing applicant's claimed mono-Arg insulin with the prior art. Applicant can be required to prove that prior art products do not necessarily or inherently possess characteristics of the claimed protein. Ex parte Gray, 10 USPQ2d 1922.

It is also noted that the specification indicates that mono-Arg insulin is known in the prior art. (See page 1, lines 25-30.)

No art rejection has been made over the methods of claims 21-23 and 25-27 because it is not known what the native conformation of mini-proinsulin would be and because the prior art of record appears to indicate that such proteins must be refolded following cleavage from a fusion protein. However, if this limitation were not present the claims would be rejected under 35 U.S.C. § 103 as being unpatentable over Markussen et al. (U.S. Patent No. 4,916,212) or Markussen et al. (EPO 163,529) either in view of Goeddel et al. (EPO 055,945), Mai et al., Grau (U.S. Patent No. 4,801,684) and Grau (U.S. Patent No. 4,639,332) essentially as applied to the claims in the prior Office action. The limitation of conditions where no crystals are formed would be met as the

prior art does not absolutely require crystallization and furthermore, the methods do not preclude additional steps where crystallization occurs. It is noted that the claimed methods "comprise" the recited steps and could include additional steps.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne P. Allen, whose telephone number is (703) 308-0666. The examiner can normally be reached on Monday-Thursday from 8:00 am to 5:30 pm. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Garnette D. Draper, can be reached on (703) 308-4232. The most convenient FAX telephone number for Art Unit 1812 is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Marianne P. Allen

MARIANNE P. ALLEN
PATENT EXAMINER
GROUP 1800